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16. ABSTRACT

A single intramuscular injection of $NiCl_2$ causes a suppression of natural killer (NK) cell activity, while a single injection of $MnCl_2$ enhances NK activity: When injected together Mn preempts the suppressive effect of Ni on NK activity.

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INTRODUCTION

Nickel (Ni) is an example of a toxic heavy metal of environmental concern which has been found to impair various components of the immune system (Smialowicz et al., 1984a) and to suppress host resistance to infection (Adkins et al., 1979). Certain Ni compounds have also been shown to be carcinogenic in man and animals (Sunderman, 1981).

During the course of our research on the effects of Ni on the immune system of mice, we discovered that natural killer (NK) cells were particularly sensitive to suppression by $NiCl_2$ (Smialowicz et al., 1984b). NK cells have been receiving increased attention in recent years because of their potential role as primary cytotoxic effector cells against tumors. These lymphocytes have been shown to be *in vivo* effectors against transplanted tumors and have been suggested to play a role against newly arising tumors (Herberman and Ortaldo, 1981).

While Ni suppresses murine NK activity, manganese (Mn) in the form of $MnCl_2$, enhances NK activity (Rogers et al., 1983 and Smialowicz et al., 1984c). The observation that Ni suppresses NK activity while Mn enhances it takes on added significance because of the results of Sunderman and McCully (1983) who showed that Mn dust inhibits the carcinogenicity of nickel subsulfide.

This paper summarizes the results of studies on the NK activity of mice injected with either $NiCl_2$ or $MnCl_2$.

METHODS AND RESULTS

Mice of several different strains were given a single intramuscular injection in the thigh on a body weight basis 24 hr prior to assay. Mice received a dose of 18.3 mg/kg Ni as $NiCl_2$ or 40 or 80 mg/kg Mn as $MnCl_2$ in saline. Saline injected mice served as controls. The Ni and Mn concentrations were determined by neutron activation analysis.

NK cell activity was determined using three different assay systems. These included the following: 1) an *in vitro* 4 hr ^{51}Cr-release assay in which spleen cells were cocultured with ^{51}Cr-labeled YAC-1 tumor target cells; 2) an *in vivo* clearance assay in which the clearance of

tumor cells from the lungs of mice was determined 4 hr after an intravenous injection of ^{125}I-labeled YAC-1 cells; and 3) an *in vivo* tumor assay in which the number of tumor foci in the lungs was determined 2-3 weeks after an intravenous injection of B16-F10 melanoma cells.

Table 1 summarizes representative results from several experiments in which the effects of Ni and Mn on NK activity were determined. A single intramuscular injection of $NiCl_2$ (18.3 mg/kg) caused a significant suppression of NK cell activity as determined by the *in vitro* ^{51}Cr-release assay. The clearance of radiolabeled tumor cells from the lungs of Ni-treated mice was also significantly reduced compared with saline controls. A single injection of 18.3 mg/kg $NiCl_2$ 24 hr before injection of B16-F10 melanoma cells significantly increased the number of resulting lung tumors compared with saline controls.

TABLE 1. Comparison of the effects of Ni and Mn on NK activity.

Treatment[a]	$\bar{x}$% ^{51}Cr Release±SE[b]	$\bar{x}$% ^{125}I Recovered[c]	$\bar{x}$ Tumors/ Lung±SE[d]
Saline	14.9 ± 1.6	0.44	6.7 ± 1.3
$NiCl_2$	7.1 ± 1.6[e]	1.15[e]	63.8 ± 7.6[e]
Saline	12.5 ± 1.3	0.71	47.5 ± 10.1
$MnCl_2$	30.5 ± 2.0[e]	0.45[e]	9.0 ± 1.5[e]
Saline	12.3 ± 0.8	-	-
$NiCl_2$	4.8 ± 1.1[e]	-	-
$MnCl_2$	21.9 ± 1.7[e]	-	-
$MnCl_2$+$NiCl_2$	23.4 ± 0.8[e]	-	-

[a] Groups of 8-10 mice were given a single intramuscular injection of 18.3 mg/kg $NiCl_2$ or 40 or 80 mg/kg $MnCl_2$.
[b] Four hour *in vitro* NK activity assay against YAC-1 cells.
[c] Four hour *in vivo* tumor cell clearance assay expressed as the geometric mean.
[d] Mice were injected intramuscularly with saline, $NiCl_2$ or $MnCl_2$ 24 hr before an intravenous injection of 10^5 B16-F10 melanoma cells.
[e] $P<0.01$, metal vs saline.

In contrast, mice injected with $MnCl_2$ displayed enhanced NK activity as measured by the in vitro ^{51}Cr release assay. The enhancement of NK activity by Mn was found to be associated with increased serum levels of interferon. Furthermore, treatment of Mn-injected mice with rabbit anti-interferon α, β but not γ completely abrogated NK augmentation (Smialowicz et al., 1984c). The clearance of radiolabeled tumor cells from the lungs of Mn-treated mice was also significantly enhanced compared with saline controls. As might be expected, Mn-treated mice had significantly fewer lung tumor foci compared with saline controls following the injection of B16-F10 melanoma cells (Table 1).

When Ni and Mn were injected concomittantly in contralateral thighs, the suppression of NK activity by $NiCl_2$ was preempted by $MnCl_2$ (Table 1). Injection of $MnCl_2$ one day prior but not one day subsequent to $NiCl_2$ also resulted in enhanced NK cell activity (Rogers et al., 1983).

DISCUSSION AND CONCLUSIONS

In addition to suppressing NK cell activity, $NiCl_2$ suppresses thymus-derived or T lymphocyte responses in the mouse (Smialowicz et al., 1984a,b). Both of these lymphocyte populations play a role in immune defenses against neoplasia. In contrast, $MnCl_2$ enhances NK cell activity as well as macrophage function, including macrophage tumoricidal activity (Rogers, et al., 1983; Smialowicz et al., 1984c,d). Mn-enhanced natural cell-mediated immune effector cell function appears to be mediated by interferon. These results taken together may provide some insights into the inhibitory effect of Mn on Ni-induced sarcomas in rats described by Sunderman and McCulley (1983). While the results are far from conclusive, they suggest that an epigenetic mechanism may contribute to Ni-induced carcinogenesis.

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